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Rejections under 35 U.S.C. § 103

Regarding Civelli et al. in view of Wetters et al.

Applicants respectfully traverse the rejection of claims 1-22 and 25-28 under 35 U.S.C. § 103(a) over Civelli et al., U.S. Patent 5,441,883, in view of Wetters et al., EMBO J. 11:551-557 (1992).

The Office Action asserts that Civelli et al. describes a method for the production of an organic molecule having a desired property which involves inherently providing a reaction mixture with at least 10-100 different organic molecules in solution in the same reaction container and causing at least one chemical reaction to take place with at least some of the different organic molecules in the reaction mixture to create a reaction mixture having one or more organic molecules different from the organic molecules in the starting mixture, followed by repetition of the reaction step to produce a final reaction mixture, which is then screened for the presence of the organic molecule having the desired property.

The Office Action concedes that Civelli et al. does not teach or suggest a method involving a random chemical reaction. However, the Office Action asserts that Wetters et al. describes a method employing a random chemical reaction, and alleges that it would have been obvious to combine the processes of the two references, substituting the random chemical reaction of Wetters et al. in the method of Civelli et al. because Wetters et al.

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allegedly reports that random mutagenesis should distribute silent mutations equally within a target cassette.

To establish a *prima facie* case, the Office must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998); *Northern Telecom v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); *In re Erlich*, 3 U.S.P.Q.2d 1011, 1016 (Bd. Pat. App. & Int. 1986). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness. In particular, the prior art references relied upon in making the present

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rejection do not provide the skilled artisan with the requisite motivation to combine their content in order to achieve the claimed invention.

If a proposal for modifying the prior art in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. See *In re Fritch*, 972 F.2d at 1265 n.12, 23 U.S.P.Q.2d at 1783 n.12972 F.2d 1260, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992) ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose."); *In re Ratti*, 270 F.2d 810, 123 U.S.P.Q. 349 (C.C.P.A. 1959) (holding the suggested combination of references improper under ' 103 because it "would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate").

Here, the passage cited from the primary reference by Civelli et al. is directed to the characterization and study of rat A3 adenosine receptor and, in particular, to amplification of two specific primers in order to determine the distribution of the A3 adenosine receptor in rat tissues. In contrast, Wetters et al. is directed to a method of random mutagenesis of CSF-1 receptor to determine which sites are critical for the induction of cell transformation. Adding random mutagenesis to the PCR amplification of two specific primers, where the amplification is

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done for the specific purpose of determining which rat tissues express the particular nucleic acid sequence amplified by the two selected primers and, therefore, is dependent on the integrity of the primer sequences would defeat the very purpose of the primary reference. Thus, the proposed modification of the secondary reference, random mutagenesis, is inappropriate for an obviousness inquiry as it renders the primary reference inoperable for its intended purpose, namely determining tissue distribution of specific sequences.

As set forth above, far from providing a motivation to combine, modifying the prior art in an effort to attain the claimed invention causes the art itself to become inoperable and destroys its intended function. In view of the lack of a *prima facie* showing of obviousness, Applicants submit that the Office has not met its burden and respectfully request withdrawal of the rejection of claims 1-22 and 25-28 under 35 U.S.C. § 103 over Civelli et al. in view of Wetters et al.

Regarding Iacobucci et al. in view of Nova et al.

Applicants respectfully traverse the rejection of claims 36-50 stand rejected under 35 U.S.C. 103(a) over Iacobucci et al., U.S. Patent 5,350,681, in view of Nova et al., U.S. Patent 6,025,129.

The Office Action asserts that Iacobucci et al. describes a method in which a group of different substrates,

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which all share a common core structure, is reacted with a group of different enzymes.

The Office Action concedes that Iacobucci et al. does not teach or suggest a method wherein the group of different substrates contain an unlimited number of different organic molecules. However, the Office Action asserts that Nova et al. describes a method of multiplexing wherein the group of different substrates contains an unlimited number of different organic molecules and asserts that it would have been obvious to combine these two references and substitute the multiplexing method of Nova et al. in the method of Iacobucci et al. The Office Action alleges that one would have been motivated to combine the references because Nova et al. allegedly reports that it is advantageous to use a matrix with memory in multiplexing protocols, such as those in which a molecule is synthesized.

Again, Applicants respectfully submit that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness. In particular, the prior art references relied upon in making the present rejection do not teach or suggest all the limitations of the claims as is required for the establishment of a *prima facie* case of obviousness. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Specifically, Iacobucci et al. is directed to a method for the synthesis of a peptide in which the reaction is carried out in solution. In particular, the reaction takes place in a

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reaction vessel containing three liquid phases: an aqueous reactant phase, an aqueous product phase, and a water-immiscible hydrophobic phase that separates the two aqueous phases. In the aqueous reaction phase, two protected peptides are reacted in the presence of a condensation enzyme, which acts as a catalyst, to form a protected, uncharged conjugate of the two reactant peptides. The product is then transported across the water-immiscible hydrophobic phase into an aqueous product phase, where it is unprotected to form a charged species that cannot diffuse across the hydrophobic phase into the reaction mixture.

Nowhere in the cited primary reference is a teaching or suggestion of a reaction mixture being created that contains a group of different enzymes representing a diversity of catalytic activities under suitable conditions with a group of different substrates to create a reaction mixture. Rather, Iacobucci et al. describes a method for the enzymatic synthesis of a single compound, a peptide, from two single reactants. One of the reactants is a single protected peptide having a C-terminal carboxylate group or a single protected N-acyl amino acid having an alpha carboxylate group. The other reactant is a single protected peptide having an N-terminal amino group or a protected amino acid having an alpha ammonium group. These two single compounds are reacted in the presence of a condensation enzyme, allowing condensation of the carboxy group of one peptide with the amino group of the other peptide to form a protected condensation product. Nowhere, does Iacobucci et al. describe the reaction of two separate groups of compounds as alleged in the Office Action.

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The deficiency in Iacobucci et al. is not cured by the combination of Iacobucci et al. and Nova et al. because Nova et al. also does not describe the reaction of a group of substrates with a group of enzymes. Rather Nova et al. describes a series of reactions in which a single molecule or a group of molecules is reacted with a single compound. For example, Figure 1 of the Nova et al. patent illustrates the process described therein. A solid support is reacted with a compound. For example, in Figure 1, the support is individually reacted with a compound A and a compound B. It is clear from the description in the patent that these compounds are reacted individually, not in a mixture. The products S-A and S-B (where S indicates the support) are combined and then separated to provide two mixtures, each containing both S-A and S-B. Each of these mixtures is then reacted with a single compound. In one instance the mixture is reacted with compound C. In another instance, the mixture is reacted with compound D. The resulting individual products S-A-C, S-B-C, S-A-D, and S-B-D are combined and then separated to provide two mixtures of these four compounds. Each of the two resulting mixtures is then individually reacted with a single compound. The mixture is either reacted with compound E or with compound F to provide eight products that are again combined and separated. The process continues in a like manner to achieve the desired mixture of products. Thus, at each step of Nova et al., a single compound or mixture of compounds is reacted with only a single compound, not a mixture of compounds.

In sum, neither of the cited references, alone or viewed in combination, teaches or suggests a method of reacting a

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group of different enzymes representing a diversity of catalytic activities under suitable conditions with a group of different substrates to create a reaction mixture, thereby producing one or more organic molecules different from the enzymes and substrates in the reaction mixture as recited in the claims. Therefore, the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness, which requires showing that the prior art references relied upon teach or suggest all the elements of the claims.

In view of the above remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 36-50 under 35 U.S.C. § 103 over Iacobucci et al. in view of Nova et al.

Regarding Civelli et al. in view of Wetters et al. and further in view of Furka et al.

Applicants respectfully traverse the rejection of claims 23 and 24 under 35 U.S.C. 103(a) over Civelli et al., *supra*, in view of Wetters et al., *supra*, and further in view of Furka et al. (International Journal of Peptide and Protein Research, (1991), Vol. 37, page 487-493).

The merit of this obviousness rejection relies upon the combination of Civelli et al. and Wetters et al. with regard to teaching or suggesting the invention of claims 1-22 and 25-28. In particular, the Office Action asserts that Civelli et al. in

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view of Wetters et al. renders obvious the method of claims 1-22 and 25-28, but concedes that these references do not describe the step of dividing the first reaction mixture into at least two subgroups, each containing less than all of the different organic molecules in the starting group. As set forth above, far from providing a motivation to combine, modifying the the cited primary reference by Civelli et al. with Wetters et al. in an effort to attain the claimed invention of claims 1-22 and 25-28 causes the art itself to become inoperable and destroys its intended function.

Furka et al. is directed to solid phase chemical reactions, whereas the other two cited references are directed to solution based reactions. In particular, Furka et al. is directed to solid phase synthesis of peptides having predetermined sequences. The basic process described by Furka et al. is similar to that discussed above with regard to Nova et al., in which a mixture of peptides attached to solid supports are reacted individually with one of two peptides, followed by mixing of the resulting products and separation into a number of groups equal to the number of different amino acids desired at a given position. Each group is then reacted with an amino acid and the process repeated.

Viewing Civelli et al. and Wetters et al. in further combination with Furka et al. does not cure the lack of a *prima facie* showing of obviousness with regard to claims 1-22 and 25-28. Consequently, Applicants submit that the Office has not met its burden and respectfully request withdrawal of the rejection

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of claims 23 and 24 under 35 U.S.C. § 103 over Civelli et al. in view of Wetters et al. and further in view of Furka et al.

Regarding Shen et al. in view of Fodor et al. and further in view of Nova et al.

Claims 29-35 stand rejected under 35 U.S.C. § 103(a) over Shen et al., U.S. Patent 3,932,498, in view of Fodor et al., Science, 251: 767-73 (1991) and further in view of Nova et al., U.S. Patent No. 6,025,129.

The Office Action asserts that Shen et al. describes a method for the production and characterization of an organic molecule having a desired property which involves reacting a group of different acid substrates with a dehydrating agent under suitable conditions to yield a first reaction mixture followed by reaction of the first reaction mixture with a reducing agent to yield a second reaction mixture, which is then reacted with an oxidizing agent to provide a third reaction mixture that is condensed to provide a fourth reaction mixture.

The Action concedes that Shen et al. does not describe a method of exposing an organic reaction mixture to light having a wavelength of about 220 nm to 600 nm to produce one or more molecules different from the substrates and agents, but alleges that Fodor et al. describes such a method. The Action further concedes that Shen et al. does not teach a method of screening the exposed reaction mixture for the presence of the organic molecule and isolating the molecule having the desired property

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from the reaction mixture, but similarly alleges that Fodor et al. describes a method of screening the reaction mixture for the presence of the organic molecule and isolating a molecule having the desired property from the reaction mixture.

The Office Action asserts that it would have been prima facie obvious to combine and substitute the steps of exposing an organic reaction mixture to light with a wavelength of about 22 nm to 600 nm to produce one or more organic molecules different from the substrates and agents of Fodor et al. in the method for production of an organic molecule having a desired property of Shen et al. because Fodor et al. allegedly reports that high-density arrays formed by light-directed synthesis are potentially rich sources of chemical diversity for discovering new ligands that bind to biological receptors and for elucidating principles governing molecular interactions.

The Office Action concedes, however, that the combination of Shen et al. in view of Fodor et al. does not teach or suggest the reaction of a group of different substrates, but alleges that Nova et al. describes a method of multiplexing wherein the group of different substrates contain an unlimited number of different organic molecules. The Office Action alleges that it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a method of multiplexing wherein the group of different substrates contain an unlimited number of different organic molecules of Nova et al. in the method for the production and characterization of an organic molecule having a desired

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property of Shen et al. in view of Fodor et al. because Nova et al. reports that the combination of matrix with memory is also advantageously used in the multiplex protocols, such as those in which a molecule is synthesized.

Applicants submit that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness, which requires showing that the prior art references relied upon teach or suggest all the elements of the claims. In particular, the combination of cited references does not teach or suggest a process for the production of an organic molecule having a desired property which includes reacting a group of different substrates, containing acids, amines, alcohols, and unsaturated compounds, with a dehydrating agent, followed by a reducing agent, followed by an oxidizing agent, followed by performing a condensation reaction and then exposing the reaction mixture to light at a wavelength of about 220 nm to 600 nm to produce one or more molecules different from the substrates and agents.

Shen et al. does not describe a method in which a group of different substrates, selected from acids, amines, alcohols, and unsaturated compounds, are reacted to yield a first reaction mixture, followed by reduction with a reducing agent, oxidation with an oxidizing agent, and condensation to produce a reaction mixture. Rather, Shen et al. describes reaction of a single compound to produce a single compound. Thus, Shen et al. does not describe a method for the production of an organic molecule, having a desired property, through a series of specific reactions

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on a group of different substrates. Further, as noted in the Office Action, Shen et al. does not describe or suggest a method of exposing an organic reaction mixture to light having a wavelength of about 220 nm to 600 nm or a method of screening the exposed reaction mixture for the presence of the organic molecule having a desired property and isolation of that molecule from the reaction mixture.

Fodor et al. does not cure the deficiencies of Shen et al. because Fodor et al. also does not describe the reaction of a group of different substrates. Fodor et al. describes solid phase chemical coupling reactions. In particular, Fodor et al. is directed to the preparation of peptides on a solid support. The surface of the solid support is exposed to light using a mask or similar means to activate reactive groups on some portions, but not on other portions, of the surface of the support. A protected molecule, such as a nucleic acid or an amino acid, is coupled to the reactive groups on the surface of the support. This "first molecule" is then deprotected and/or the unreacted surface activated by exposing the support containing the first molecule to light using a mask to direct which molecules will be deprotected or activated. The support is then reacted with a single second protected molecule which is coupled only to those first molecules which are deprotected or to the newly activated groups on the surface of the support. Repetition of this process allows for directed synthesis of particular peptides on the surface of the support. The process is illustrated in Figure 1 at page 768. From this illustration, it is apparent that only a single molecule is reacted with the substrate product at each

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reaction step. Therefore, the combination of Shen et al. and Fodor et al. does not teach or suggest the claimed series of reactions with a group of different substrates as recited in the instant claims.

The addition of Nova et al. to the combination of Shen et al. and Fodor et al. does not render the claimed invention obvious for the reasons that follow. Nova et al. is directed to the use of specialized matrices as solid supports for chemical and biochemical syntheses, such as the production of nucleotide or peptide molecules. In particular, Nova et al. does not teach or suggest a process for the production of an organic molecule having a desired property which includes reacting a group of different substrates, containing acids, amines, alcohols, and unsaturated compounds. Applicants respectfully submit that the combination of specifically recited substrates is meaningful language in the context of the claimed invention and, to render obvious the invention, any combination of cited references must recite this particular combination of substrates rather than contain a general statement. In the absence of showing such a teaching or suggestion of all claim elements in the combined references, a *prima facie* case of obviousness cannot be established. Consequently, the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness, which requires showing that the prior art references relied upon teach or suggest all the elements of the claims.

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Finally, the syntheses described in Nova et al. require the immobilization of at least one molecule to the surface of the matrix followed by reactions involving the immobilized molecule. One having ordinary skill in the art at the time of the invention would not have had a reasonable expectation that the types of reactions described in Shen et al. could be performed using the matrices described in Nova et al., but would instead have recognized that the reactions described in Shen et al. would either not occur or be would be hindered if the starting material was immobilized to the surface of a matrix. Thus, the proposed modification of the secondary reference by Nova et al. is inappropriate for an obviousness inquiry as it renders the primary reference inoperable for its intended purpose. Again, far from providing a motivation to combine, modifying the prior art in an effort to attain the claimed invention causes the art itself to become inoperable and destroys its intended function.

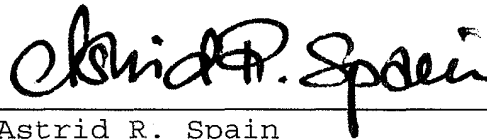
In view of the above remarks, Applicants respectfully submit that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness. In particular, the prior art references, in combination, do not teach or suggest each element of the claimed invention and, furthermore, do not provide the skilled artisan with the requisite motivation to combine their content in order to achieve the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Shen et al. in view of Fodor et al. and further in view of Nova et al.

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CONCLUSION

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney or Cathryn Campbell.

Respectfully submitted,



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